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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/990,711
Filing Date: November 14, 2001
Appellant(s): BAKER ET AL.

Christopher De Vry
For Appellants

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12 August 2008 appealing from the Office action mailed 10 December 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

As discussed in the Appeal Brief, U.S. Serial Number 09/941,992 is directed to PRO341 polypeptides, which is related to the instant application claiming antibodies that bind PRO341 polypeptides. Also, the Board is advised that there are numerous applications filed by Genentech relying upon the gene amplification assay for utility which are under similar rejections and/or appeals.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellants' statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Hittelman, W. "Genetic Instability in Epithelial Tissues at Risk for Cancer" Ann. NY Acad. Sci., vol952 (2001), pp. 1-12.

Pennica, D. et al. "WISP genes are members of the connective tissue growth factor family hat are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors" Proc. Natl. Acad. Sci., vol95 (December 1998), pp. 14717-14722.

Konopka, J.B. et al. "Variable expression of the translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" Proc. Natl. Acad. Sci. USA, vol83 (June 1986), pp. 4049-4052.

Sen, S. "Aneuploidy and cancer" Curr. Opin. Oncol., vol12 (2000), pp. 82-88.

Godbout, R. et al. "Overexpression of a DEAD box protein (DDX1) in neuroblastoma and retinoblastoma cell lines" J. Biol. Chem. vol273, no. 33 (14 August 1998), pp. 21161-21168.

Li, R. et al. "Identification of putative oncogenes in lung adenocarcinoma by a comprehensive functional genomic approach" Oncogene vol25 (2006), pp. 2628-2635.

Hanna, J.S. and Mornin, D. "HER-2/neu Breast Cancer Predictive Testing" Pathology Associates Medical Laboratories (1999), pp. 1-2.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

The independent claim (claim 119) is directed to an antibody that specifically binds the polypeptide of SEQ ID NO: 20. Dependent claims are also presented to specific forms of such an antibody, namely, monoclonal, humanized, fragment, and labeled. The specification discloses the polypeptide of SEQ ID NO: 20, also known as PRO341. The specification discloses how to make the type of antibodies recited in the claims. It is noted that the question of whether or not the claimed antibodies have utility and are enabled depends entirely upon whether or not the polypeptide they bind has

utility and enablement. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed antibodies and the polypeptide they bind. See Appeal Brief (received 12 August 2008), p. 4, beginning of arguments.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO341 had a ΔCt value of at least 1.0 for three out of fourteen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides, and the antibodies that specifically bind them, are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

First, there are several problems with the data provided in this example. Only

three out of the fourteen lung cancer samples tested positive. Therefore, if a sample were taken from an individual with lung cancer for diagnosis, ***it is more likely than not that this assay would yield a false negative result***. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO341 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO341 is a diagnostic probe for lung cancer unless it is clear that PRO341 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of lung tumor samples had tested positive, the data have no bearing on the utility of the claimed *antibodies that specifically bind PRO341 polypeptides*. In order for PRO341 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO341 mRNA or PRO341 polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be

presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Hanna and Mornin (1999, Pathology Associates Medical Laboratories) provide another important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide (or antibody) can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO341 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments,

as directed by the art. Since the asserted utility for the claimed antibodies that bind polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The *general* concept of gene amplification's lack of correlation with mRNA/polypeptide overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general lack of correlation between gene amplification and mRNA/polypeptide overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes***

are not over-expressed unless they provide a selective growth advantage to the cell (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO341 confers any growth advantage to a cell, and thus it cannot be presumed that the polypeptide is overexpressed because the genomic DNA including the gene being studied gene is amplified. Thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies that bind polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the***

genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased polypeptide levels***, absent evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO341.

Therefore, data pertaining to PRO341 genomic DNA do not indicate anything significant regarding the claimed antibodies that bind PRO341 polypeptides. The data do not support the specification's assertion that PRO341 polypeptides and antibodies can be used as a cancer diagnostic or therapeutic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO341 polypeptide recited in the claims is overexpressed in any cancer to the extent that the polypeptide or the antibodies could be used as cancer diagnostic or therapeutic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO341 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO341 **antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., and Hanna and Mornin, all of which are of record and have been previously discussed), the rejections are properly maintained.

Claims 119-123 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

From p. 4 to p. 5 of the Appeal Brief, Appellants provide a summary of their arguments. Appellants begin by reviewing the data presented in Example 170, which has been analyzed in detail in the rejection above. Specifically, Appellants argue that the skilled artisan would expect that the gene amplification data for PRO341 gene implicates that the PRO341 polypeptide is overexpressed. This has been fully considered but is not found to be persuasive because of the evidence that gene

amplification is not correlated with polypeptide overexpression (Pennica et al., Hanna and Mornin, Godbout et al., Li et al., and Sen). Also, since PRO341 gene was only amplified at a ΔCt value of 1.12 to 1.33 for three out of fourteen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers, if a new, putative lung sample were tested for PRO341 amplification, it is more likely than not that the PRO341 diagnostic test would yield a false negative result.

At p. 4 of the Appeal Brief, Appellants refer to the Goddard declaration as evidence that a 2-fold amplification in the gene amplification is significant and indicates that the gene is useful as a marker for diagnosis of cancer, monitoring cancer development, and/or measuring efficacy of cancer therapy. This has been fully considered but is not found to be persuasive because it is not an accurate description of the Goddard declaration. The declaration addresses whether the ΔCt values are significant, and does not speak to whether or not gene amplification correlates with polypeptide levels, which is the critical question at issue in this case. The Goddard declaration will be addressed in greater detail below, at the point in the arguments where Appellants provide more extensive arguments regarding the same.

At the bottom of p. 4 of the Appeal Brief Appellants argue that even if there were no correlation between gene amplification and increased mRNA/polypeptide overexpression , a polypeptide encoded by such a gene would still have utility. Appellants point to the Ashkenazi declaration and the Hanna and Mornin reference as establishing that simultaneous testing of gene amplification and gene product overexpression leads to a better determination of a suitable therapy for the tumor. The

Ashkenazi declaration under 37 CFR 1.132 filed 24 October 2003 and the Hanna and Mornin reference are insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because the declaration and reference support the rejections in admitting that amplified genes may not correlate with gene product overexpression. It is also important to note that the specification never suggests using such information for tumor categorization or to develop more suitable therapies. In fact, other than a general assertion that a polypeptide and its antibodies can be used therapeutically, no "suitable therapy" is suggested for cancers that may be represented by the samples assayed in the instant specification. Classification of tumors and identification of such therapies is another example of the type of further experimentation required to confirm a real-world utility. Thus, the asserted utility is not substantial.

At p. 5, first paragraph, of the Brief, Appellants argues that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At p. 5, second and third paragraphs, Appellants argue that one of ordinary skill

would find it credible that the claimed antibodies have utility as markers for lung tumors based on the gene amplification assay, and that the specification teaches how to make and use such antibodies without undue experimentation. This has been fully considered but is not found to be persuasive. As discussed above in the restatement of the rejections, data pertaining to PRO341 genomic DNA do not indicate anything significant regarding the PRO341 polypeptide recited in the claims. The data do not support the specification's assertion that PRO341 polypeptides and their antibodies can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO341 polypeptides are overexpressed in any cancer to the extent that they or their antibodies could be used as cancer diagnostic or therapeutic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO341 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO341 **polypeptides and antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies. In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., and Hanna and Mornin, all of which are of record and have been previously discussed), the rejections are properly maintained.

Appellants' detailed arguments begin at the bottom of p. 5 of the appeal brief. Appellants begin with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 9 of the Brief, Appellants review Example 170, and refer to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 24 October 2003 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.173 to 2.514 fold amplification in three out of fourteen lung cancer samples is significant, and whether such data have any relevance to the claimed subject matter, i.e., PRO341 antibodies. The significance can be questioned based on the weakness of the data and the strength of opposing evidence. In the instant case, only a very small percentage of the cancer samples tested positive for PRO341 gene amplification. Also, the controls used were not matched, non-tumorous lung samples but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al.). This art, as well as the Sen, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to

whether or not the claimed antibodies have utility and enablement based on a presumption of polypeptide overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues. Since the claims under examination are directed to antibodies that bind polypeptides, not genes, this question is critical.

At p. 11 of the Brief, Appellants take issue with the examiner's concern regarding false negatives. Appellants urge that not all tumor markers are associated with all tumors, and that some markers are useful for identifying rare malignancies. Appellants argue that such markers have great value in diagnosis and prognosis. This has been fully considered but is not found to be persuasive. PRO341 gene was amplified in three lung tumor samples, namely, LT16, LT17, and LT21 (see p. 550). According to Table 8 on p. 546, LT16 and LT17 are lung squamous cell carcinomas, whereas LT21 is a lung large cell carcinoma. There is nothing in common between LT16, LT17, and LT21 (type of cell, stage, etc.) that is not shared by the other lung tumor samples that would indicate that PRO341 corresponds to a rare malignancy. Therefore, the evidence does not support Appellants' position.

At p. 12 of the Brief, Appellants argue that the examiner's concern regarding aneuploidy is not damaging to utility and enablement. Appellants point to the Ashkenazi declaration and the Hittelman et al. publication as supporting Appellants' position that PRO341 is still useful in diagnosing pre-cancerous lesions or cancer itself. Appellants urge that there is utility in identifying genetic markers in epithelial tissues at cancer risk.

This has been fully considered but is not found to be persuasive. Appellants' arguments contradict the asserted utility in the specification, i.e., that gene amplification indicates that the polypeptide and its antibodies are cancer diagnostic markers. Nowhere in the specification is it asserted that the polypeptide or its antibodies can be used as a marker for cancer risk diagnosis. Furthermore, the Ashkenazi declaration under 37 CFR 1.132 filed 24 October 2003 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because: the declaration supports the examiner's position that gene amplification cannot be assumed to correlate with increased expression of the gene.

Beginning at p. 12 of the Appeal Brief, Appellants argue that a *prima facie* case of lack of utility has not been established. Appellants again urge that the proper legal standard is "more likely than not." Appellants criticize Pennica et al. as being limited to individual WISP genes, and that no general trends can be concluded therefrom. Appellants point to the correlation between WISP-1 gene amplification and polypeptide overexpression. At p. 13 of the Appeal Brief, Appellants criticize Konopka et al. on the same grounds, i.e., that it is limited to a specific result and does not teach anything about gene amplification and polypeptide over-expression in general. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica et al. and Konopka et al. constitute evidence that it cannot be assumed that amplified genomic DNA for a single gene results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect with

respect to the general concept of whether or not gene amplification correlates with increased mRNA/polypeptide expression. Finally, Sen and Hittelman constitute evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

At p. 15, Appellants take issue with the Godbout et al. reference, arguing that it was never claimed that PRO341 was similar to the DDX1 gene of Godbout et al. Appellants argue that Godbout et al. show good correlation between gene amplification and polypeptide expression levels. Appellants assert that selective advantage to the cell is not the only mechanism by which genes impact cancer. Appellants urge that structure/function data are not a requirement for utility. This has been fully considered but is not found to be persuasive. Appellants' assertions are in direct contradiction to the statements made in the Godbout et al. evidence. Specifically, Godbout et al. state that ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell."*** Appellants have provided no evidence to contradict this. Godbout et al. do show a good correlation between gene amplification and polypeptide over-expression, but *only* when the gene provides a selective growth advantage to the cell. No evidence has been brought forward that PRO341 provides such an advantage.

At pp. 15-16 of the Appeal Brief, Appellants criticize Li et al. Appellants urge that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Appellants refer to the supplemental information accompanying the Li et al. article, enclosed with the

Brief. Appellants urge that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above), and thus Hyman et al. supports the examiner's position. Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

> Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At p. 16 of the Appeal Brief, Appellants take issue with the examiner's analysis of Li et al. Appellants urge that the examiner has misinterpreted the methodology, and that the cited material pertains to inclusion criteria of probes for defining amplicons. Appellants quote from Li et al. referring to the 1.4 ratio. Appellants state that the examiner acknowledges that the 2-fold amplification would apply to some of the samples. Appellants conclude that the examiner has not established that a correlation does not exist in samples based solely on this threshold. This has been fully considered but is not found to be persuasive. It is unclear what point Appellants are trying to make. While not limited to such, Li et al. clearly include genes that are

amplified at a ratio of two or more. Li et al. clearly state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased polypeptide levels***, absent evidence that the polypeptide has biological relevance in cancer. Appellants have not established that the genes in the 2-fold or more amplification level had correlation with polypeptide over-expression whereas those between 1.4 and 2.0 lacked correlation. Godbout et al., Sen, and Hittelman also speak to the general lack of correlation between gene amplification levels and polypeptide ever-expression for genes which are not known to provide a selective growth advantage to the cell.

Beginning at p. 16 of the Appeal Brief, Appellants argue that it is more likely than not that amplified genes have increased mRNA. Appellants point to Example 170 of the specification as disclosing that amplification is associated with overexpression of the gene product, indicating that the polypeptides and their antibodies are useful targets for therapeutic intervention and diagnostic determination. This has been fully considered but is not found to be persuasive. Several pieces of evidence contradict this statement by showing that gene amplification cannot be assumed to correlate with gene product

overexpression. See Pennica et al., Konopka et al., Hittelman, Sen, Godbout et al., Hanna and Mornin, and the Ashkenazi declaration, all of record.

At pp. 16-17 of the Appeal Brief, Appellants refer to Orntoft et al., Hyman et al., and Pollack et al. as evidencing that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO341 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant

specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer.

At p. 17, second paragraph, of the Brief, Appellants argues that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At the third paragraph of p. 17 of the Brief, Appellants argue that the examiner appears to disregard the evidence of the articles relied upon by Appellants based on misinterpretations of their teachings. Appellants argue that the articles lend support that an amplified gene is more likely than not also overexpressed. Appellants urge that this interpretation would be viewed as reasonable and credible by the skilled artisan. Appellants argue that the "more likely than not" standard is a much lower standard than a "necessary" or "accurate" correlation. Appellants assert that the examiner has not cited any evidence or advanced any arguments as to why Appellants' statement of overexpression of polypeptide would not be credible. This has been fully considered but is not found to be persuasive. Patentable utility must be credible, specific, and substantial. Credibility and specificity have not been questioned. However, the

asserted utility is not substantial because it would require further research to reasonably confirm a real world use. The rejection is supported by several pieces of evidence that show that gene amplification cannot be assumed to correlate with polypeptide overexpression. See Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., Li et al., Hanna and Mornin, and the Ashkenazi declaration. Since the effective filing date of July 1998, no evidence has been brought forth on the record as to whether or not the polypeptide level of PRO341 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies that bind polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

Beginning at the fourth paragraph of p. 17 of the Brief, Appellants argue that whether or not PRO341 is in a gene cluster region of a chromosome is not relevant, since Orntoft et al. allegedly did not limit their studies to such clusters, and Hyman et al. and Pollack et al. did gene-by-gene analysis. At p. 18 of the Brief, Appellants provide a more detailed analysis of Hyman et al. and Pollack et al. This has been fully considered but is not found to be persuasive. Regarding Hyman et al., Appellants quote from Hyman et al. at the top of p. 18 of the arguments, wherein Hyman et al. found that up to 44% of highly amplified genes were overexpressed. This is less than half. Thus, regardless of methodology, Hyman et al. support the rejection that it is more likely than not that an amplified gene fails to correlate with polypeptide overexpression. Pollack et al. add a cautionary note in their discussion section that there may be differences in

correlations depending on what tissue is being studied. Specifically, at p. 12967, Pollack et al. refer to Platzer et al., who find a poor correlation between DNA amplification and overexpression. Pollack et al. discuss how this difference may be de to different methodology, but also may be due to real biological differences between breast and colon tumors (p. 12968). It is noted that PRO341 is reported in the specification as being amplified in lung carcinomas, whereas Pollack et al. studied breast cancers. Li et al. studied lung carcinomas, and found poor correlation. Li et al. include a similar cautionary note that their results may be tissue-dependent (p. 2629). Therefore, Li et al. is the more relevant piece of evidence, in that it concerns the same type of cancer for which the specification asserts PRO341 is a marker. Also interesting is that Pollack et al. used a normal female leukocyte DNA control from a single donor rather than normal breast tissue (matched tissue control), whereas Platzer et al. compared colon cancer samples to normal colon epithelium, and Li et al. compared lung carcinoma samples with normal lung tissue.

At pp. 18-19 of the Brief, Appellants argue that, contrary to the examiner's characterization of the articles, Hyman et al. reported a clinical association between HOXB7 amplification and poor patient prognosis, thus suggesting that the research was relevant to identifying probes that can be used as cancer diagnostics. Appellants also point to Pollack et al.'s final paragraph as implying a diagnostic utility. This has been fully considered but is not found to be persuasive. Hyman et al. and Pollack et al. relied on significant further research to identify a very small number of genes that had potential as cancer markers. For example, Hyman et al. identified 270 specific amplified

genes, but only identified one, HOXB7, as being potentially associated with poor prognosis. Hyman et al. only suggested such in view of other research that had already linked HOXB7 to cancer. See second paragraph on p. 6244, wherein Hyman et al. refer to six other research papers regarding HOXB7 and cancer, including experiments wherein HOXB7 was transfected into normal cells and induced cell proliferation and tumorigenicity. Pollack et al.'s final paragraph contains several cautionary notes about their findings, including a specific statement at p. 12968 that "this finding cautions that elevated expression of an amplified gene cannot alone be considered strong independent evidence of a candidate oncogene's role in tumorigenesis….This highlights the importance of high-resolution mapping of amplicon boundaries and shape..on a large number of samples, in addition to functional studies." Thus, the art clearly directs the skilled artisan to further experimentation before identifying any amplified gene or its expression product as a diagnostic marker or a target for therapeutic intervention, clearly supporting the rejection's findings that the asserted utility is not substantial.

Beginning at p. 19 of the Brief, Appellants argue that, even is a *prima facie* case of lack of utility has been established, it should be withdrawn based on the totality of the evidence. Appellants again draw attention to the Ashkenazi declaration, urging that gene amplification even without polypeptide overexpression is useful in that it assists the clinician in tumor classification and selection of treatment modalities that are specific to the tumor, thus avoiding excess cost and side effects. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been

required to do the testing to reasonably confirm whether or not the PRO341 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO341 antibodies are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO341. For example, neither the specification nor the prior art discloses an agent that targets PRO341 that is useful for cancer therapy. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At p. 20 of the Brief, Appellants argue that the opinion of Dr. Ashkenazi is supported by the Hanna and Mornin reference. Appellants urge that the publication evidences that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Appellants argue that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna and Mornin support the rejection, in that Hanna and Mornin show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed antibodies is not in currently available form, and requires further

experimentation to reasonably confirm the suggested use, the asserted utility is not substantial. Finally, it is no small matter to go from information regarding polypeptide expression levels in a tumor to designing a therapeutic regimen specific to the polypeptide expression profile. In Hanna and Mornin, Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO341 polypeptide. Identifying a drug specific for PRO341 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO341 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

At p. 20, Appellants urge that the examiner has misread Hanna and Mornin, and quote from Hanna and Mornin that, in general, FISH and IHC correlates well. Appellants urge that only a subset of tumors show discordant results. This has been fully considered but is not found to be persuasive. Hanna and Mornin do not appear to disclose the percentage of tumors having a correlation and those not having a correlation. However, Hanna and Mornin clearly caution the clinician not to assume that HER-2/neu polypeptide is overexpressed based on gene amplification tests, since administering Herceptin to patients not overexpressing HER-2/neu was harmful. Thus, the art directs the skilled artisan to do the further experimentation on the expression levels of the polypeptide.

At p. 20, third paragraph, Appellants argue that the specification demonstrates

PRO341 gene amplification in three lung tumors and concludes that PRO341 is a tumor associated gene like HER-2/neu. Appellants urge that gene amplification, in the majority of cases, influences mRNA and polypeptide levels, allegedly based on the art. Appellants conclude that the skilled artisan would reasonably expect that PRO341 polypeptide is overexpressed in lung tumors. This has been fully considered but is not found to be persuasive. PRO341 gene was not amplified in eleven out of fourteen lung tumors tested. Therefore, screening a new lung tumor sample with a PRO341 probe would more likely than not provide a false negative result. Furthermore, the preponderance of the evidence clearly indicates that gene amplification cannot be assumed to correlate with polypeptide overexpression. See Pennica et al., Konopka et al., Hittelman, Sen, Godbout et al., Li et al., Hanna and Mornin, an even the Ashkenazi declaration and the Hyman et al. article. The art directs the skilled artisan to perform further experiments to determine whether or not a polypeptide is overexpressed in cancer tissue. Thus, since further experimentation is clearly required to reasonably confirm the asserted utility, the asserted utility is not substantial.

At the top of p. 21 of the Brief, Appellants argue that the examiner improperly views the further testing described in the Ashkenazi declaration as further characterization f the PRO341 polypeptide itself. Appellants assert that the experimentation described is only further characterization of the tumor, not the polypeptide. Appellants argue that the PRO341 polypeptide and its antibodies are useful in tumor categorization, enabling the physician to select a treatment modality that holds the most promise for successful treatment of a patient. This has been fully

considered but is not found to be persuasive. The tissue specific pattern of expression of a polypeptide is definitely a feature of the polypeptide itself. The determination of such is a form of characterizing the polypeptide. Furthermore, no treatment modalities specific to PRO341 have been disclosed in the specification or prior art. The identification of such would require significant further research, thus also indicating that the asserted utility is not substantial.

At pp. 21-22 of the Brief, Appellants conclude by arguing that, based on the asserted utility for PRO341 in lung cancer diagnosis, the reduction to practice of the polypeptide of SEQ ID NO: 20, the disclosure of protocols for making chimeric PRO polypeptides and antibodies such as those claimed and for recombinant expression of PRO341, the disclosure of protocols for making PRO341 antibodies, and the gene amplification assay, the skilled artisan would know exactly how to make and use the claimed antibodies for diagnosis of lung cancers. Appellants urge that testing would have been routine and not undue. This has been fully considered but is not found to be persuasive. The rejection is supported by the preponderance of the evidence. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Sen). The specification does not assert a utility for PRO341 as a biomarker for damaged, pre-cancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellants (Pennica et al., Godbout et al., Li et al.). Contrary to Appellants' assertions, the state of the art indicates that gene amplification is not generally associated with overexpression

of the encoded gene product, as evidenced by Sen, Pennica et al., Godbout et al., Hyman et al., and Li et al. The declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with polypeptide overexpression but Dr. Ashkenazi indicates that this is not always the case. Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO341 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since significant further research would have been required of the skilled artisan to reasonably confirm that PRO341 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the PRO341 polypeptides or antibodies can be used as cancer therapeutics, since there is no evidence that PRO341 plays a role in cancer formation or progression such that inhibiting PRO341 would result in effective cancer therapy. In the absence of information regarding whether or not PRO341 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO341 **polypeptides and antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the

claimed antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Hearing

It does not appear that Appellants have requested an oral hearing at this time. However, if an oral hearing is requested, the examiner requests the opportunity to present arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Elizabeth C. Kemmerer/

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